Our Thanks to Hoechst-Roussel

We recognize with appreciation Hoechst-Roussel for pledging support to the Endowment Fund for The Journal of Investigative Dermatology, *which will be used to support the growth and continued success of the Journal. This support will certainly strengthen and perpetuate the partnership between the pharmaceutical industry and basic and clinical investigators in cutaneous biology.*

We salute Hoechst-Roussel for their contribution to the Endowment Fund and for their continued support of clinical and investigative dermatology.

D.A.N., Denver, CO.

In This Issue . . .

Lela A. Lee

The Network Theory of Autoimmunity in Bullous Pemphigoid

In 1974 Jerne proposed a network theory of the immune system in which antibodies bearing idiotypic determinants interact with anti-idiotypic antibodies. The anti-idiotypic antibodies may themselves interact with anti–anti-idiotypic antibodies. The effect of this chain of interactions is to regulate the immune response. Such a network has since been demonstrated, and there is evidence to indicate that regulation of the immune response by anti-idiotypic networks may be clinically significant. Idiotypes have been used not only to study the regulation of the immune response but also to map V region genes.

To review the terminology, an "idiotope" is a potentially antigenic portion of the V region of an antibody, that is, a portion of the V region that may itself be bound by an antibody. An "idiotype" refers to the set of idiotopes on a given antibody or on a group of related antibodies. Idiotopes and idiotypes are defined serologically. An idiotope should not be confused with the antigen-binding cleft (also called paratope) of an antibody. Although it is possible for a given idiotope to be in or near the antigen-binding site, it is also possible for an idiotope to be distant from the antigen-binding site.

Idiotypic networks have been described in certain autoimmune diseases, including lupus erythematosus, thyroid diseases, and myasthenia gravis. In immune responses, certain idiotypes predominate. (The reason for this is not known. It may represent a selection over many generations of the most effective V regions for a given immune response.) There is evidence that the predominant idiotypes expressed in some diseases may correlate with the clinical course, and the presence of anti-idiotypic antibodies has been associated in some autoimmune diseases with clinical remissions.

In this issue, Joyce Rico, La Donna White, Scott Bartow, and Russell Hall, from Duke University, describe an idiotype expressed in a significant percentage of bullous pemphigoid (BP) antisera. This is the first demonstration of such an idiotype in a skin-specific autoimmune disease. Using epidermal sheets, antibodies binding the basement membrane zone were extracted from the serum of a patient with BP. Mice were immunized against these antibodies and mouse monoclonal antibodies were generated. A monoclonal antibody was found that not only bound BP antibodies from the patient whose antibodies were used to generate the monoclonal but also bound BP antibodies from a substantial number of other patients (18 of 50 BP antisera tested).

As they detail in their manuscript, there are several lines of investigation opened by these studies. First, it can be determined whether idiotypes expressed in the sera in BP are also bound in the skin. Second, certain idiotypes may correlate with the clinical presentation or course. If so, this would be particularly useful information, because circulating levels of BP antibodies as a whole do not correlate well with the clinical course. Third, the anti-idiotypic regulatory network and its association with disease course can be examined. Fourth, V region gene markers for disease susceptibility may be identified. Analysis of V region gene markers may also lead to an understanding of what initiates the immune response in BP.

Why might certain idiotypes relate to disease susceptibility or clinical course in BP? As is the case for other diseases, the answer to this is not known. One possibility is that particular idiotypes arise during the utilization of specific V region genes. These V region genes might encode for antibodies which recognize particular sites on the BP antigen. Antibodies bearing these idiotypes may be important in initiating, maintaining, and regulating the immune response against the BP antigen. Patients who have antibodies which express these particular idiotypes thus may have the potential under the right circumstances to develop BP.

Whatever the outcomes of future studies of the idiotypic network in BP, it is likely that such studies will lead to a better understanding of the pathogenesis of BP and the regulation of the immune response in BP.

0022-202X/91/$03.50

The Biosynthesis of Type VII Collagen

Type VII collagen is the major structural protein of anchoring fibrils. The epidermolysis bullosa diseases involving anchoring fibrils illustrate the importance of these structures in the integrity of the skin. Although much is known about the biochemical properties of type VII collagen, little is known about its biosynthesis and about the biosynthesis of anchoring fibrils. An article in this issue by Adrian König and Leena Bruckner-Tuderman, from University Hospital in Zurich, examines the biosynthesis of type VII collagen in cell cultures and in "skin equivalents" (stratified keratinocytes overlying fibroblasts embedded in a gel of collagen types I and III). When both keratinocytes and fibroblasts were present in cultures, type VII collagen was abundantly produced and could be extracted from the cultures in substantial amounts. The production of such large amounts of type VII collagen under culture conditions is one of the major achievements of this study. Little type VII collagen was produced with either keratinocytes alone or fibroblasts alone, an indication that interactions between keratinocytes and fibroblasts are crucial to the production of significant amounts of type VII collagen. Whether cell-cell interactions, soluble mediators, or both contribute to enhance the synthesis of type VII collagen has not yet been established.

The skin equivalents were used to examine the appearance and location of type VII collagen, laminin, and type IV collagen. Laminin and type IV collagen were found in linear deposits at the interface of the epithelium and mesenchyme, a location identical to that seen in normal skin. Type VII collagen, however, appeared in the lower layers of the epithelium rather than at the epithelial-mesenchymal interface. The location of type VII collagen in the skin equivalents implies that keratinocytes in the lower epithelium were the major producers of type VII collagen. It also implies that anchoring fibrils were not formed. It is not clear whether anchoring fibrils simply need more time to form, or whether other factors currently lacking in the skin equivalents are needed to direct the formation of anchoring fibrils. Ultimately, all the factors controlling the generation of anchoring fibrils will need to be determined. This study is an important contribution to that process. By optimizing conditions for the generation of type VII collagen, it provides a means for examining a critical early step in the formation of anchoring fibrils.

Langerhans Cells Harbor Human Immunodeficiency Virus-1 (HIV-1)

An envelope protein of HIV-1 binds to the CD4 cluster differentiation antigen, and that binding is the initial step in the predominant route of entry of HIV-1 into cells. The only resident cells of the epidermis that express CD4 are Langerhans cells (LC) and, as such, they are the major candidate for harboring HIV-1 within the epidermis. In 1987, Tshachler and co-workers, using immunohistochemical techniques, described HIV-1 in LC. However, those findings were not confirmed by later studies from other groups. This controversial issue has been re-examined by Giovanna Zambruno, Luigi Mori, Alessandra Marconi, Nicola Mongiardo, Bruno De Rienzo, Umberto Bertazzoni, and Alberto Giannetti, from the University of Modena and the Institute of Biochemical and Evolutionary Genetics of CNR in Pavia. They hypothesized that HIV-1 DNA and proteins might be present in the skin in amounts too low to detect consistently by morphologic techniques. In order to increase sensitivity of detection, they used the polymerase chain reaction (PCR) to examine HIV-1 proviral DNA in LC from clinically normal skin of HIV-1 – infected patients. From split-thickness skin slices, epidermal cell suspensions were prepared. Using the monoclonal antibody OKT6 and a technique involving rosetting of cells attached to beads, the epidermal cell suspensions were segregated into LC-enriched and LC-depleted populations. Ninety-five percent of cells from the LC-enriched population were HLA-DR$^+$ and therefore probably LC, and 0.1% of cells from the LC-depleted population were HLA-DR$^+$. To verify by another technique that the rosetted cells were LC, normal controls were examined using transmission electron microscopy. All cells surrounded by beads in the LC-enriched population had the morphology of LC by electron microscopy. With PCR, HIV-1 proviral DNA was found in the LC population of seven of nine patients and none of the normal controls. In the LC-depleted populations, HIV-1 proviral DNA was found in one of nine patients (the one positive sample gave only a weak signal) and none of the normal controls. These data, then, provide strong evidence that LC can serve as a reservoir of HIV-1 in the skin. Because the presence of proviral DNA but not mRNA or protein was measured in these studies, further studies will be needed to determine whether LC can be productively infected by HIV-1.